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Adhesion

Its Role in Inflammatory Disease

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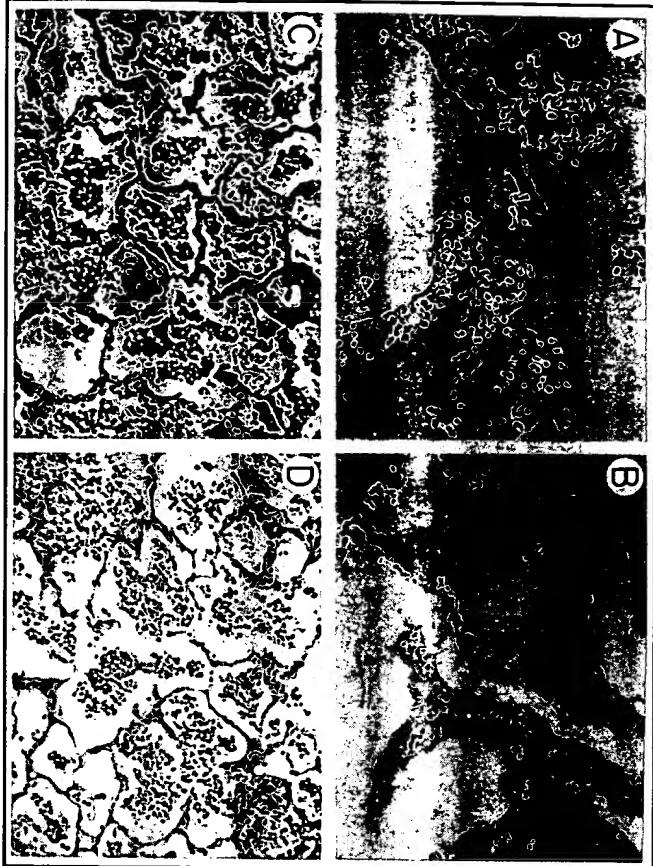


Figure 6-2. CD18-dependent and -independent mechanisms of neutrophil emigration. Neutrophil migration in response to *S. pneumoniae*-induced inflammation was assessed in a control animal or an animal pretreated with the CD18 MAb 60.3 (2 mg/kg). **A**, *S. pneumoniae*-containing sponge in control animal showing infiltration of sponge by neutrophils. **B**, *S. pneumoniae*-containing sponge in animal pretreated with MAb 60.3, showing complete absence of neutrophils. **C**, lung of control animal after instillation of *S. pneumoniae*, showing accumulation of neutrophils in alveoli. **D**, lung of MAb 60.3-treated animal (same animal as in **B**) following instillation of *S. pneumoniae*, showing accumulation of neutrophils in alveoli. Adapted from Doerschuk, C.M., Winn, R.K., Coxson, H.O., and Hartan, J.M. (1990) *J. Immunol.* 144, 2327-2333 with permission.

hours prior in order to elicit a macrophage-rich exudate, then the CD18 MAb only minimally inhibited *S. pneumoniae*-induced emigration (36%), although it still inhibited *E. coli* emigration by nearly 90%. If the "primed" peritoneum was washed to remove macrophages prior to instillation of *S. pneumoniae* organisms, neutrophil emigration was again inhibited by nearly 90% by the CD18 MAb. Finally, instillation of macrophages obtained from protease peptone-treated animals into normal animals significantly reduced the inhibition produced by the CD18 MAb (48%). Overall, these results demonstrate that the CD18-independent mechanism of emigration that is observed in the pulmonary microcirculation in response to *S. pneumoniae* organisms can be induced in the systemic microcirculation by maneuvers that augment the number of macrophages in the peritoneal cavity. The macrophage-generated product(s) elicited by *S. pneumoniae* organisms and the adhesion molecules involved in this CD18-independent pathway remain to be identified.

ICAM-1

Intercellular adhesion molecule-1 (ICAM-1, CD54)^{77,78} and ICAM-2⁷⁹ are ligands for CD11a/CD18. ICAM-1 is expressed at low levels on endothelium *in vivo*, and is up-regulated in response to inflammatory stimuli. ICAM-2 is constitutively expressed on endothelium. CD11a/CD18 recognizes both ICAM-1 and ICAM-2. Studies by Smith et al.⁸⁰ and by Diamond et al.⁸¹ indicate that ICAM-1 is also a ligand for CD11b/CD18. Monoclonal antibodies to ICAM-1 have been demonstrated to inhibit lymphocyte and neutrophil emigration to tissues in several models of inflammation and immune reaction^{82,83} (Table 6-1).

L-Selectin

The L(leukocyte)-selectin (LECAM-1, LAM-1) was first described in the mouse as the MEL-14 antigen, the "homing" receptor for lymphocyte binding to high endothelial venules of peripheral lymph nodes.¹ Lewinsohn et al.⁸⁴ showed that the MEL-14 antigen was also present on granulocytes and lymphocytes and that the MEL-14 MAb inhibited the binding of neutrophils and monocytes to inflamed high endothelial venules in tissue sections and at sites of acute inflammation in the skin. Subsequently, Jutila et al.⁸⁵ showed that MEL-14 also inhibited neutrophil accumulation in inflamed peritoneum. These observations using the MEL-14 MAb were confirmed by Watson et al.⁸⁶ using a soluble immunoglobulin chimera containing the murine homing receptor extracellular domain (LEC-IgG). Administration of LEC-IgG significantly decreased the number of neutrophils that migrated to the peritoneum in response to the inflammatory irritant thioglycolate. Watson